Immunotherapy for metastatic cancer patients: the current status, limitations, obstacles and future directions

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Background & current status

Immunotherapy (IO), especially a subgroup called immune checkpoint inhibitors (ICIs) has revolutionized the treatment of a variety of cancers in past few years.

ICIs include anti-PD-1 & anti-PD-L1 antibodies, as well as CTLA-4 inhibitors. Clinical trials showed that ~15% to 40% of cancer patients (sometime more) respond to ICIs (1,2). Time for response can be longer than those with traditional chemotherapy. Hence IOs may not be very appropriate for patients who require immediate cytoreduction for symptom relief or those near end-of-life.

During initial phase of IO treatment, new lesions can occur as a result of inflammatory process, but they subsequent regress. This is called "pseudoprogression". It occurs in ≤5% of cases (3). Some patients who do not meet the criteria of objective response on traditional RECIST criteria may achieve prolonged periods of stable disease that are clinically significant. This leads to the proposal of using iRECIST criteria in IO studies. On the other hand, ~10% (4) of patient may exhibit hyperprogression phenomenon (doubling of tumor growth rate within ≤12 wks after start of treatment). Some researchers suggested that hyperprogression might be more commonly seen in elderlies, and may be associated with certain gene mutations (2,4). If hyperprogression occurs, prognosis is usually poor. Switching to alternative systemic therapy or best supportive care may be considered if appropriate.

Despite promising results published, most of the patients succumb after treatment. Only a minority of patient achieved durable response and have prolong survival. The majority of irAEs occur within first 4 months of ICI treatment, but irAEs can occur months after completion of IO (5). Some irAEs are devastating, long lasting and fatal. Severe flare up of psoriasis, pneumonitis, colitis, cardiac toxicities, neurological irAEs and graft rejection after transplant have been reported.

In general, the overall toxicities leading to discontinuation treatment due to irAEs are higher with CTLA-4 inhibitors like ipilimumab than anti-PD1 therapy using nivolumab or pembrolizumab (6). Immune related colitis/gastrointestinal irAEs & hypophysitis may be more common in CTLA-4 inhibitors. On the other hand, thyroid related irAEs, vitiligo, pneumonitis ± graft rejection may be more frequent in anti-PD1 therapy (2). The safety data for PD-L1 inhibitors are still maturing. Details of grading of various irAEs & their managements have been published (2,7) and will not be discussed in details here. Patients who develop grade 3–4 irAEs need prompt recognition, treatment and close monitoring of response to systemic steroid ± other immunomodulatory agent(s). Tailing down of steroid should be slow, at least over 4–6 wks to avoid recurrence of irAEs.

At present, some clinical trials are exploring the role of combinations IOs with other IOs, novel agents, chemotherapy and radiotherapy. Higher treatment related toxicities are expected in combination treatments.

Median progression-free survival (PFS) & median overall survival (OS) might be good enough outcome

measures when patients only survive for months. However, for patients who achieved long term durable response from IO, provision of PFS & OS in pre-specified clinically meaningful time-points such as 1, 2 & 3 years using landmark analysis (8), as well as health-related quality of life data with utility scores, will be valuable to guide treatment decision. Unfortunately, not much data are available in these aspects. The KEYNOTE-006 trial by Petrella *et al.* (9) shows that measuring QOL data & utility scores are feasible, especially in well designed, large, pre-planned prospective studies.

Limitations & obstacles

At present, we lack reliable biomarkers to help us select which patients will benefit from IO *vs.* which will not (4). Tumor response may occur in patient with not much PD-L1 expression. Tumor heterogeneity and different techniques used in the assays can partly account for the problem. There is still a lot to be learnt concerning the mechanisms of action of individual agent, and drug resistance. The most appropriate agents, optimal sequence and duration of treatment is not yet known (6).

The drugs remain very expensive (4). Not many patients or health care systems can afford such high costing for long (10), especially if the disease being treated has a high incidence/prevalence in society. Some patients are forced to discontinue treatment because they run out of money.

Reporting of outcome indicators of immunotherapies are not comprehensive enough. Quality of life data are often lacking. Larger prospective trials with longer follow up are required.

The safety profiles of other immunotherapies are still maturing. There is not much data on the safety profile of immunotherapies in some special populations such as elderlies ≥70–75 years old, those with other medical co-morbidities/auto-immune disease or history of transplant. Nevertheless, patients with active, uncontrolled autoimmune diseases on high dose immunosuppressants are not good candidates for IO. They may be more prone to various irAEs, with lower response rate & inferior survival.

The study carried out by Lau *et al.* (11)

This is a retrospective, single-centered study. It included 50 cancer patients in Hong Kong given anti-PD1 therapy during the period of June 2016 to June 2017. All of these patients had regular imaging assessment at an interval of

3 months or more frequently. FU period was <3 years. Tumor response was evaluated by the traditional RECIST criteria version 1.1. Toxicities were reported according to the National Cancer Institute CTAE version 4.0. This study is one of the very early studies reporting treatment outcome & toxicity profile in a heterogeneous group of metastatic cancers managed in an oncology center outside clinical trial setting. One of the special points is that the authors included number of palliative care consultation & use of hospice service in data collection. Patient up to 87 years old were included (almost half of them >65 years old, although the exact age distribution pattern was not shown). The study showed that age alone is not a limitation for receiving IO; at least it is feasible in cases when the treating physician considers appropriate. Seventy-six percent (38 out of 50 patients) had an ECOG score of 0 or 1, while 24% (12 out of 50 patients) got an ECOG score of 2 or 3. Half of the patients are on 3rd line palliative treatment or beyond. Sixty-four percent of patients are symptomatic at initiation of therapy. Only 14% (7 out of 50 patients) got renal cell carcinoma or urothelial cancers. Patient with head & neck cancer, lung cancer, gastrointestinal cancer and hepatocellular cancer were included, but there were no melanoma patients. No patients with inflammatory bowel disease nor history of transplant were included. Three patients (6%) got history of Graves' disease. Although the number of patients was only 50, such case-mix provided additional information on outcomes & toxicity profiles of patients on anti-PD1 therapy whom oncologists encountered in daily practice. Thus this study is very important & influential in providing data in real world situations, unmasking the potentials of severe irAEs of anti-PD1 therapy. It also revealed that only a minority of patients benefits from IO with durable response. IOs are not a panacea for everybody.

Ten (20%) of patient experienced grade 3 or 4 irAEs. Three patients (6%) underwent invasive procedures of either biopsy or endoscopy for diagnosis & management of irAEs. Eight patients (16%) received systemic corticosteroids for at least 1 month. Two patents (4%) required the addition of IV immunoglobulin for the management of G3/4 irAEs. Four patients (8%) developed a secondary infection and two patients (4%) died as a result. Seven (14%) discontinued anti-PD1 therapy permanently due to grade 3/4 toxicities. The development of grade 3/4 irAEs requiring in-patient management, with a median duration of hospitalization of 6.5 days (range, 1 to 38 days). One patient developed severe hypophysitis, admitted ICU for care & subsequently died. Seven (14%) developed immune-related dermatitis; one

of them got severe toxic epidermoid necrolysis leading to ICU say for over 1 month. One patient developed grade 3 immune-related nephritis and require ICU stay for hemodialysis.

Among patients with irAEs, 36% (9 out of 25 patients) showed either complete or partial remission. On contrary, 96% (24 out of 25 patients) without experiencing irAE at ≤3 months of initiation of anti-PD1 therapy showed static disease or progressive disease.

At the assessment of the study, thirty-five mortalities (70%) had occurred. Eighteen patients (36%) had received palliative care (PC) consultations, and twelve patients (24%) died in hospice units. Patients seems to be more likely to receive PC consultations if ≥65 years old or having a baseline ECOG status of 2 or above. This echoes with the observation study by Yeh *et al.* (12) which shows a relative low utilization of palliative care service among patient under oncology care at Johns Hopkins Hospital in USA. These patients were sent to subacute rehabilitation unit, hoping that their general condition will improve and further oncological treatment could be given. Unfortunately, majority of patients died soon without receiving any anti-cancer therapies. Most of them died in non-hospice unit settings. This raises the concern whether patients on IO are referred late to palliative care workers, with their need for palliative care not adequately addressed.

Kaplan-Meier survival curves were provided in the article. Log rank test comparing the PFS & OS in those with & without experiencing irAEs showed no statistically significant difference in PFS, but a trend of improved OS (P=0.05) was observed. This is not uncommon in patients who achieved long term stable disease control (8). The curve for OS seems to show clear separation at around 1 year in patients with any grade irAEs compared with those with no irAEs. A significant minority of patients with any grade irAEs seems to remain alive at the end of the study.

Future directions

There is still a long way to success of cancer treatment.

Mechanisms of cancer development, progression, tumor cell microenvironment and drug resistance need to be elucidated (4). Trials on various combination treatments are on the way. Other newer classes of IO like CAR-T cell therapy etc. warrants further evaluation.

More post-marketing data on the safety profiles of IO in elderly & frail patients with wider spectrum of auto-immune disease are required.

We need to search for biomarkers that can help us to select the most appropriate person for treatment and help prediction of good/unsatisfactory treatment outcomes (4). It will be good if we can identify patients prone to treatment related side effects and develop strategies to counteract it without jeopardizing treatment outcome of ICIs.

The turn over time for laboratory testing of biomarkers should be fast with high throughput (4). Besides the potential of reducing cost per test, this can ensure availability of timely result to guide treatment decision.

Well designed, large prospective clinical trials to find the optimal drug regimens & duration of treatment, as well as methods to reduce treatment related toxicities are urgently needed. They should include more comprehensive outcome measures other than response rate & median PFS/OS. If possible, quality of life data should be incorporated in clinical trials as well as daily clinical practice for more comprehensive evaluation of patients. Researchers, statisticians and health economists experienced in such trial designs & analyses should be consulted at conceptualization of trials. Appropriate & validated questionnaires should be chosen to answer the clinical & research questions, preferably using multi-dimensional tools incorporating the generic ± disease-specific ± condition specific aspects (13), as well as utility scores (14) & quality-adjusted year (QALY) analysis. The whole batch of QoL questionnaires should be of reasonable length to ensure patient compliance during data collection. Well documented scoring method & interpretation guide should be available (15). Longitudinal follow up of data at appropriate time-points should be arranged if possible. Missing data should be managed according to standard protocols.

The final goal is personalized cancer therapy and cancer immunoprevention (4).

Education of clinicians and clients/family about possible signs & symptoms of various irAEs are important. Both parties should have realistic goals rather than a false hope of miracle cure, without addressing the potential harms of IO (16). As serious irAEs can occur months after completion of IO, high level of alertness & suspicion are required. Hospice clinicians need to be aware of the wide spectrum of irAEs that might mimic infections or progression of cancer. Fatigue can be due to endocrinopathies as such hypothyroidism, hypoadrenalism and hypophysitis. Management of patients with recent history of receiving IO might not be as minimalistic as in the past. Blood tests, imaging, endoscopic examinations and biopsy should be ordered when appropriate. Close communication and back

up from parent oncology team and other relevant specialties should be facilitated.

Choosing the wrong patient to start IO (e.g., near end-of-life) might render patients & carers suffer & regret, and might jeopardize their chance of receiving timely palliative care (12). The decision process of giving systemic treatment or continue best supportive care could be difficult. Both clinicians and patient/family may have undergone significant psychosocial & financial turmoil. Oncologists with additional qualifications in palliative care may help in these situations. The model of embedded or integrated palliative care within oncology units (17-21) may be particularly suitable in these situations. This will ensure smooth transition of active oncological care to comfort care near end-of- life care, and promote the feeling of non-abandonment.

To deal with an aging population with exponential rise in drug costing and disease management, health care policy makers and government should prioritize goals according to society need, cost effectiveness & cost-utility analysis etc. This calls for collaboration between medical & economic researchers. Novel drug reimbursement program should be developed after negotiation with relevant stakeholders including representatives from insurance company & pharmaceutical companies (4,10,22). It is important to ensure accessibility of relevant drugs to needy persons at a society affordable price, yet keeping the momentum of pharmaceutical companies for new drugs discovery which will benefit mankind. When the patency of drug has expired, biosimilar can be developed to further lower the drug expenditure.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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